Assessment of D-dimer for ruling out peripherally inserted central catheter-associated upper extremity venous thrombosis: a diagnostic accuracy study

Wanli Liu
Xiangya Hospital Central South University
Lianxiang He
Xiangya Hospital Central South University
Wenjing Zeng
Xiangya Hospital Central South University
Liqing Yue
Xiangya Hospital Central South University
Jie Wei
Xiangya Hospital Central South University
Shuangshuang Zeng
Xiangya Hospital Central South University
Xiang Wang
Xiangya Hospital Central South University
Zhicheng Gong (506017215@qq.com)
Xiangya Hospital Central South University https://orcid.org/0000-0002-7315-7856

Research

Keywords: D-dimer, deep vein thrombosis, superficial venous thrombosis, PICC, sensitivity and specificity, venous thrombosis

Posted Date: September 2nd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-70098/v1

Abstract

Background: With the extensive use of peripherally inserted central catheter (PICC), PICC-associated venous thrombosis (VT) has become one of the most important complications in the hospital. To reduce unnecessary color Doppler ultrasound (CDU) or imaging tests, D-dimer values are usually used to exclude VT. There is little evidence for the usefulness of the D-dimer level as an independent diagnostic marker for excluding PICC-associated VT.

Objectives: To examine the effectiveness of D-dimer concentration to be used as an independent diagnostic marker for excluding PICC-associated UEVT. Design: A retrospective case cohort study. Settings: One teaching hospital in Hunan, China. Participants: In total, 281 subjects who underwent CDU and D-dimer values after PICC placement were eligible.

Methods:The patients were categorized into the DVT unlikely group (<2 points) and the DVT likely group (≥2 points) according to their modified Wells score post PICC placement, before extubation. After the Wells score was determined, the patients underwent a D-dimer test and CDU within 7 days after D-dimer test.

Results: 281 patients were included in the final analysis. Of them, 180 patients had D-dimer value <0.5 mgL-1. There were 39 patients with upper extremity venous thrombosis identified via CDU and 78.3% with negative predictive value of D-dimer for PICC-associated VT (95% CI: 71.7–83.7%). The negative predictive value of D-dimer for SVT was 91.0% (95% CI: 85.4–94.6%), which was higher than that for DVT (84.9%, 95% CI: 78.7–89.6%) and for VT in the cancer population (80.0%, 95% CI: 73.2–85.4%) and the non-cancer population (60.0%, 95% CI: 35.7–80.2%).

Conclusion: the D-dimer concentration should not be used as a diagnostic index to rule out PICC-associated VT to avoid missed diagnosis of PICC-related venous thrombosis, which may cause adverse consequences or may even be life-threatening.

1. Introduction

In patients requiring infusion of corrosive drugs or long-term infusions, peripherally inserted central catheter (PICC) is a convenient alternative to central venous catheter (CVC). PICCs are easy to place, can be nurse-led, and do not have risks associated with CVC insertion [1]. However, PICCs have a risk of developing upper extremity isolated superficial venous thrombosis (UESVT) and deep venous thrombosis (UEDVT). PICC-associated UESVT and UEDVT are defined as SVT and DVT, respectively, in the same or adjacent vein as the recently placed PICC. Concurrent SVT and PICC-associated UEDVT are also considered DVT. Meanwhile, prior DVT or isolated SVT in the same arm prior to PICC insertion is considered non-PICC-associated VT. UEDVT commonly affects inpatients and accounts for half of hospital-acquired DVT [2][3, 4], which usually leads to treatment disruption, obvious scarring and occlusion of the deep veins of the upper extremity, impaired venous reflux and subsequent establishment of venous access, and increased hospital stay and cost [5][6] and may even cause pulmonary embolism [1][3]. Despite few studies on PICC-associated UESVT, the association between SVT and DVT is known to be variable. DVT and pulmonary embolism occur in 18.1% and 6.9% of SVT patients, respectively [7].

The standard diagnostic modality for PICC-associated VT is color Doppler ultrasound (CDU). However, its use remains controversial. The American Society of Hematology 2018 guidelines for the diagnosis and management of venous thromboembolism recommend the D-dimer test as the initial screening modality for patients with low venous thromboembolism (VTE) risk (unlikely) as it reduces the need for diagnostic imaging. Negative D-dimer may exclude UEDVT and indicate the needlessness of other tests or anticoagulation therapy [1].

D-dimer, the minimal degradation product of fibrin, is produced by fibrinolytic protein hydrolysis of fibrin. It has been established as a sensitive biomarker for activation of the fibrinolytic system[8]. In VTE events, D-dimer levels can rise abnormally; accordingly, the diagnosis of VTE can be assisted by determining the D-dimer levels. D-dimer tests include enzyme-linked immunosorbent assay (ELISA), latex agglutination assay, and whole blood agglutination assay. ELISA method has higher sensitivity (> 95%) and negative predictive value than the other two methods, and the results are more objective. Among patients determined to have a low risk for DVT, a D-dimer level of < 0.5 mgL^{-1} accurately ruled out DVT without the need for CDU or other imaging tests and helped avoid unnecessary anticoagulant treatment[1][9][10][11][12][13]. Further, the risk of VTE in these patients was very low over the next 3 months (< 1%) [11][12][13]. However,the majority of patients who undergo PICC placement in China are cancer chemotherapy patients[14].Moreover, PICC-associated UEVT is different from the usual venous thrombus, as the former presents primarily as a mural thrombus[2][3, 4]. The different study population and the different type of VT may affect D-dimer levels, and the question of whether they are also sensitive to rule out PICC-associated UEVT remains unclear. Thus, this study aimed to investigate whether the D-dimer concentration could also be used as an independent diagnostic marker for excluding PICC-associated UEVT.

2. Methods

2.1 Study design

This was a retrospective case cohort study. The patients were categorized into the DVT unlikely group (< 2 points) and the DVT likely group (≥ 2 points) according to their modified Wells score post PICC placement, before extubation. After the Wells score was determined, the patients underwent a D-dimer test

(ELISA method)and CDU within 7 days after D-dimer test.To examine the effectiveness of D-dimer concentration to be used as an independent diagnostic marker for excluding PICC-associated UEVT.

2.2 Study settings

The study was conducted between October 1, 2017, and October 1, 2019 on the all wards of a teaching hospital in Hunan, China. The teaching hospital is a 3500-bed urban tertiary facility, which is consistently ranked as a top hospital in South China and provides state-of-the-art diagnosis and treatment services.

2.3 Study participants

- Inclusion criteria were as follows: 1) patients aged ≥ 18 years; 2) patients with peripherally inserted central catheters inserted via the upper arms; 3) < 2 points on the modified Wells score; 4) patients who underwent CDU and D-dimer values after PICC placement. Exclusion criteria were as follows: 1) PICC-associated lower extremity venous thrombosis (LEVT); 2) a duration of > 7 days between D-dimer examination and CDU;and 3)outpatient management.Subjects were excluded from the study for incomplete data. Data, including basic demographic characteristics, PICC, test results, disease course, and medications, were collected using the standard form in the Reasonable Safety Infusion Monitoring System of Xiangya Hospital of Central South University.

2.4 Ethical considerations

The study was approved by the ethics committee of Xiangya Hospital of Central South University (201907733) and was conducted according to the Helsinki Declaration of Ethical Principles for Medical Research involving Human Subjects.

2.5 Outcome measurements

2.5.1 Diagnosis of venous thrombosis

After determining the Wells score, the patients underwent D-dimer test and CDU, with the latter conducted within 7 days after the former. Subsequent D-dimer test was conducted using the ELISA method [11]. D-dimer results were defined as negative (i.e., D-dimer < 0.5 mgL^{-1}) and positive (i.e., D-dimer ≥ 0.5 mgL^{-1}) (Fig. 1). The main criteria for the diagnosis of VT were as follows [15][17]: for probe after compression, the lumen cannot be compressed; the blood flow signal in the lumen is filled with defects; solid return can be seen in the lumen sound; disappearance or weakening of the spent response; phase change in the loss of the blood spectrum; and weakening or disappearance of the blood flow of the distal limb by squeezing. Deep veins of the upper limb included brachial vein, axillary vein, subclavian artery, internal jugular vein, and brachial vein [15, 16]. Superficial veins of the upper limb included cephalic and cubital median veins and the basilic veins [2][17] [18]. In cases of inconclusive CDU diagnosis, a second CDU was conducted by another physician. Differences in diagnosis between the two CDU physicians were resolved according to the opinion of a third CDU physician. If the diagnosis cannot be established on CDU, venography or computed tomography was used.

2.5.2 Outcomes

The main outcome of interest was CDU results of UESVT and UEDVT. PICC-associated UESVT and UEDVT was defined as events after the PICC catheter placement date and before extubation. D-dimer levels were determined after catheterization. Because the risk of VTE is dynamic and changes during hospitalization [2], only D-dimer data collected within 7 days prior to CDU were analyzed. The primary outcome measure was the failure rate of the primary diagnostic strategy. This was defined as the proportion of patients in whom PICC-associated VT was ruled out based on assessment of lower VTE probability and negative D-dimer levels but were diagnosed with PICC-associated VT on CDU. The outcome indexes were PICC-associated VT, PICC-associated DVT, and PICC-associated SVT. The patients were further divided into two subgroups, namely, the cancer and non-cancer subgroups.

2.6 Statistical analysis

The reliability and effectiveness of D-dimer level as an independent biomarker for PICC-associated VT was evaluated according to its sensitivity, specificity, negative predictive value, and positive predictive value and the need for ultrasonography examinations. The patients were divided into the PICC-treated group, PICC-treated cancer group, and PICC-treated non-cancer group. The 95% confidence intervals (CI) were presented. All statistical analyses were performed using SPSS statistical software version 18.0.

3. Results

In total, 7454 patients underwent PICC placement during the study period. Of them, 3592 patients without CDU screening were excluded. Of the 3862 patients who underwent CDU screening, 3093 developed VT and 769 did not, yielding an incidence rate of 19.9%. After excluding 3212 patients with no D-dimer data within 7 days before CDU, 266 patients with LEVT, and 103 patients with Wells score ≥ 2 points, 281 patients were included in the final analysis (Fig. 2). The patients' clinicodemographic characteristics are shown in Table 3. Overall, 180 patients (64%, 95% CI: 58.2–69.4%) had positive fixed D-dimer results, whereas 101 patients (36%, 95% CI: 30.6%-41.8%) had negative D-dimer results (Fig. 3). Thirty-nine patients were referred for CDU despite having a negative D-dimer result, of whom one was diagnosed with VT. The reasons for undergoing CDU despite a negative D-dimer result are summarized in Table 4. Table 5 shows the results of the diagnostic value of D-dimer levels. The results of CDU were used as reference. The accuracy, sensitivity, positive-likelihood ratio, negative-likelihood ratio, and positive predictive value of D-dimer levels as well as the number of patients who required ultrasonography examinations of D-dimer were not high. The negative predictive value of PICC-associated SVT in the cancer group was 91.7% (95% CI: 86.0–95.2%), while the negative predictive value of PICC-associated VT in the non-cancer group was 60.0% (95% CI: 35.7–80.2%). Overall, the negative predictive value of D-dimer for SVT was 91.0% (95% CI:

85.4–94.6%), which is higher than that of DVT at 84.9% (95% CI: 78.7–89.6%). The negative predictive value in the cancer group was 80.0% (95% CI: 73.2–85.4%), which is higher than that in the non-cancer group at 60.0% (95% CI: 35.7–80.2%).

Table 4
Clinicodemographic characteristics of the patients

	All patients N = 281	No-VT patients N = 200	DVT patients N = 53	SVT patients N = 28
Age (years), median (IQR)	44.9 (26.5)	42.7 (45.8)	51.6 (15.5)	47.3 (26.8)
Female sex, n (%)	131 (46.6)	95 (47.5)	27 (50.9)	9 (32.1)
Cancer	231 (82.2)	169 (84.5)	41 (77.4)	21 (75.0)
Infusion of corrosive/stimulant drugs	248 (88.3)	176 (88)	48 (90.6)	24 (85.7)
Consciousness	241 (85.8)	178 (89)	43 (81.1)	20 (71.4)
Hypertension	23 (8.2)	16 (8)	6 (11.3)	1 (3.6)
Diabetes mellitus	5 (1.8)	4 (2)	0 (0)	1 (3.6)
Coronary disease	11 (3.9)	9 (4.5)	2 (3.8)	0 (0)
Positive history of thrombus	3 (1.1)	1 (0.5)	0 (0)	2 (7.1)
Normal limb movement	242 (86.1)	176 (88)	45 (84.9)	21 (75)
Positive history of catheterization	16 (5.7)	13 (6.5)	2 (3.8)	1 (3.6)
With normal international normalized ratio	233 (82.9)	172 (86)	41 (77.4)	20 (71.4)
Normal thrombin time	240 (85.4)	175 (87.5)	43 (81.1)	22 (78.6)
Normal D-dimer level before catheterization	183 (65.1)	139 (69.5)	31 (58.5)	13 (46.4)
Normal fibrinogen level	155 (55.2)	112 (56)	29 (54.7)	14 (50)
Normal white blood cell count	181 (64.4)	130 (65)	30 (56.6)	21 (75)
Normal platelet count	185 (65.8)	128 (64)	35 (66)	22 (78.6)
Normal hemoglobin count	120 (42.7)	90 (45)	23 (43.4)	7 (25)
Normal glutamic-pyruvic transaminase level	220 (78.3)	156 (78)	42 (79.2)	22 (78.6)
Normal glutamic-oxalacetic transaminase level	201 (71.5)	147 (73.5)	37 (69.8)	17 (60.7)
Normal creatinine level	236 (84)	171 (85.5)	42 (79.2)	23 (82.1)
Cooperating with tube placement	241 (85.8)	176 (88)	44 (83)	21 (75)
Normal vital signs during catheterization	254 (90.4)	184 (92)	47 (88.7)	23 (82.1)
Normal amount of bleeding during puncture	272 (96.8)	193 (96.5)	51 (96.2)	28 (100)
One-time successful puncture	252 (89.7)	183 (91.5)	45 (84.9)	24 (84.7)
Catheterization vein is the basilic vein	240 (85.4)	174 (87)	42 (79.2)	24 (85.7)
X-ray positioning T5-T7	274 (97.5)	196 (98)	50 (94.3)	28 (100)
No catheter displacement	223 (79.4)	161 (80.5)	36 (67.9)	26 (92.9)
No other PICC-associated complications	270 (96.1)	192 (96)	51 (96.2)	27 (96.4)
*IQR, interquartile range				

Table 5
Diagnostic performance of the different groups (n = 281)

	VT			DVT			SVT	
	All patients	Cancer group	Non-cancer group	All patients	Cancer group	Non-cancer group	All patients	Cancer group
Sensitivity								
TP/(TP + FN)	42/81	29/62	13/19	28/53	20/41	8/12	14/28	9/21
Estimate (%)	51.9	46.8	68.4	52.8	48.8	66.7	50.0	42.9
95% CI	41.2–62.4	34.9–59.0	46.0–84.6	39.–65.66	34.3–63.5	39.1–86.2	32.6–67.4	24.5–63.5
Specificity								
TN/(TN + FP)	141/200	132/169	9/31	141/200	132/169	9/31	141/200	132/169
Estimate (%)	70.5	78.1	29.0	70.5	78.1	71.0	70.5	78.1
95% CI	63.8–76.4	71.3–83.7	16.1–46.6	63.8–76.4	71.3–83.7	53.4–83.9	63.8–76.4	71.3–83.7
Negative predictive value								
TN/TN + FN	141/180	132/165	9/15	141/166	132/153	9/13	141/155	132/144
Estimate (%)	78.3	80.0	60.0	84.9	86.3	69.2	91.0	91.7
95% CI	71.7–83.7	73.2–85.4	35.7–80.2	78.7–89.6	80.0–90.9	42.3–87.3	85.4–94.6	86.0–95.2
Positive predictive value								
TP/TP + FP	42/101	29/66	13/35	28/87	20/57	8/30	14/73	9/46
Estimate (%)	41.6	43.9	37.1	32.2	35.1	26.7	19.2	19.6
95% CI	32.5–51.3	32.6–55.9	23.1–53.6	23.3–42.6	24.0–48.1	14.2–44.5	11.8–29.7	10.7–33.2
Positive likelihood ratio								
Sensitivity/(1 – specificity)	0.519/(1–0.705)	0.468/(1–0.781)	0.684/(1–0.29)	0.528/(1–0.705)	0.488/(1–0.781)	0.667/(1–0.710)	0.5/(1–0.705)	0.429/(1–0.781)
Estimate (ratio)	2.0	2.1	1.0	1.8	1.68	2.3	1.7	1.5
Negative likelihood ratio								
(1 – sensitivity)/specificity	(1–0.519)/0.705	(1–0.468)/0.78	(1–0.684)/0.29	(1–0.528)/0.705	(1–0.488)/0.781	(1–0.667)/0.710	(1–0.5)/0.705	(1–0.429)/0.78
Estimate (ratio)	0.7	0.7	1.1	0.7	0.7	0.5	0.7	0.7
Required ultrasonography examinations†								
TP + FP/TP + FN + FP + TN	101/281	66/231	35/50	87/253	57/210	30/43	73/228	46/190
Estimate (%)	35.9	28.6	70.0	34.4	27.1	69.8	32.0	24.2
95% CI	30.5–41.7	23.2–34.7	56.2–80.9	28.8–40.4	21.5–33.5	54.9–81.4	26.3–38.3	18.7–30.8

CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive; VTE, venous thromboembolism

4. Discussion

Diagnostic guidelines for DVT recommend using D-dimer levels to initially screen for the risk of DVT before using CDU[8]. In this study, we investigated whether the D-dimer concentration could be used as a key diagnostic marker for excluding PICC-associated VT. We evaluated patients with a PICC who had a modified Wells score of DVT < 2 points (DVT unlikely) and D-dimer < 0.5 mgL^{-1} and found that a large proportion of these patients had PICC-associated VT. These findings indicate that the D-dimer levels do not accurately reflect the risk for DVT. This is contrary to previous results showing that the D-dimer level can accurately rule out DVT. In these previous studies, the overall negative predictive values of the D-dimer level for DVT ranged from 99.3–99.8% [19][20][21]. This difference in results may be due to the dissimilarities between the current study and previous studies. First is the study population. Here, we evaluated a specific PICC population, whereas the majority of patients who undergo PICC placement in China are cancer chemotherapy patients[14]. VT events in cancer patients are usually associated with or triggered by vascular access devices. Some studies reported that 30% of all cancer patients had associated VT [3][22–25][26][27]. Some tumors are known to secrete proteolytic factors, and we speculate that some patients with malignancies and DVT have normal D-dimer

levels because of accelerated degradation of D-dimer [10]. Moreover, some chemotherapeutic drugs may also induce the degradation of D-dimer. Overall, the complexity of various factors in cancer patients, ranging from complications to drugs used for the cancer itself, may affect the sensitivity of D-dimer as a biomarker [10]. The second largest population of patients who undergo PICC placement is the critically ill. In this study, non-cancer patients were mainly from the neurology and neurosurgery departments. The age of these patients, thrombotic burden and fibrinolytic activity, duration of symptoms, previous VTE and inflammatory status, and use of anticoagulants may affect the accuracy of D-dimer levels. The negative predictive value of D-dimer in the non-cancer group was lower than that in the cancer group (60.0% [95% CI: 35.7–80.2%] vs. 80.0% [95% CI: 73.2–85.4%]).

Second, the type of VT is different. Due to the difference in pathogenesis and clinical processes between UEDVT and LEDVT [28][29], we only evaluated UEVT directly or indirectly caused by PICC. Some studies have shown that approximately 75% of UEDVT cases is associated with indwelling vascular catheters [28] [29]. This association is not surprising as catheter insertion leads to endothelial damage, occupies the vein lumen (promoting venous stasis), and is often required in patients with hypercoagulability because of intercurrent illness or malignancy. Thus, placement of these devices satisfies the Virchow's triad, leading to increased risk of VTE [30]. PICC is placed in a much smaller vein than in CVC, and the risk of DVT in PICC is 2.5 times higher than that in CVC [3]. A case cohort study reported a 13-fold increased risk of thrombosis in patients receiving PICC [31]. Usually, PICC-associated VT is clinically asymptomatic. In a recent randomized controlled clinical trial of PICC-DVT using CDU screening, it was found that up to 75% of patients with catheter had VT, but only 4% of image-diagnosed patients with thrombosis developed clinical symptoms [32]. Concurrently, PICC-associated VT is unique, with most types being attached to wall thrombosis. This may be one of the important reasons for the lower negative predictive value of D-dimer level for diagnosing PICC-associated VT in this study.

4.1. Study Strengths

The advantages of our research include the use of the Reasonable Safety Infusion Monitoring System, which increases data accuracy owing to its forward-looking design and the structured, standardized collection of data. Further, all the D-dimer test results were confirmed using CDU within 7 days. To reduce the bias, the type of thrombus was divided into PICC-associated VT, PICC-associated DVT, and PICC-associated SVT. Each type had positive and negative indicators of a certain proportion of samples, and the results were relatively reliable. To evaluate the impact of cancer on VT and to reduce the impact of confounders, we also divided the population into all inpatients, cancer patients, and non-cancer patients.

4.2. Study limitations

This study also has some limitations. First, the single-center design may limit the generalizability of our findings. Further, our cutoff time was patient extubation, and follow-up data were not analyzed. As a retrospective study, our data may underestimate the true number of cases of PICC-associated SVT and DVT because our institution does not have a systematic CDU screening protocol. In addition, our population was limited only to the patients with a PICC, and further analysis in non-cancer patients was not conducted. Finally, diagnostic bias was not evaluated, which may lead some clinicians lean toward using CDU for diagnosing PICC.

4.3. Implications for practice

According to this study, the D-dimer level as an independent biomarker has low negative predictive value for PICC-associated VT in low-risk patients identified according to the modified Wells score. The D-dimer concentration should not be used as a diagnostic index to rule out PICC-associated VT to avoid missed diagnosis of PICC-related venous thrombosis, which may cause adverse consequences or may even be life-threatening.

Declarations

Conflict of interest

None.

Funding

Funded by the Finance Department Project of Hunan Province, People's Republic of China (No. [2019] 60)

Ethical approval

Approved by the Ethics Committee of Xiangya Hospital of Central South University (201907733)

Acknowledgments

We are particularly grateful to the the Reasonable Safety Infusion Monitoring System of Xiangya Hospital of Central South University for providing technical and personnel support.

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Figures

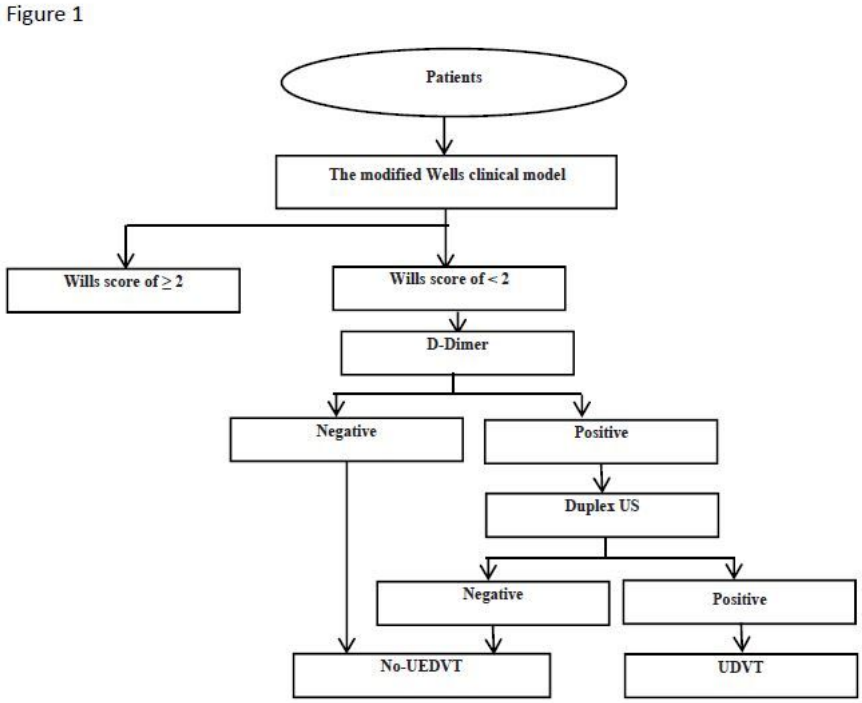

Figure 1

Flowchart for recommendations(American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism)

Figure 2

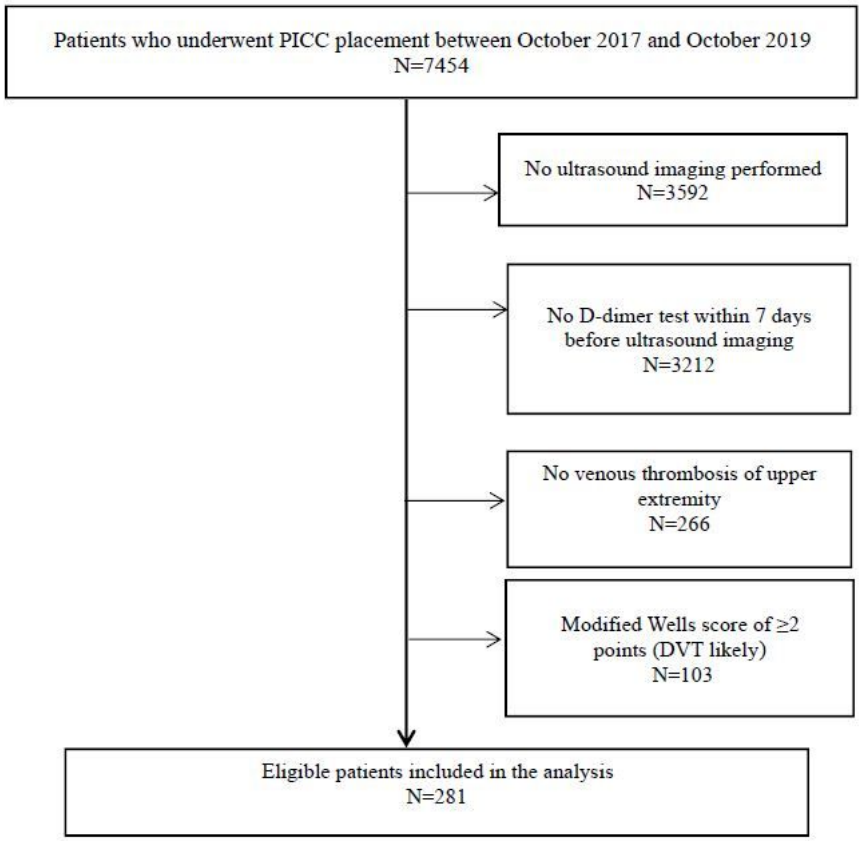

Figure 2

Flow diagram of study structure. DVT, deep vein thrombosis

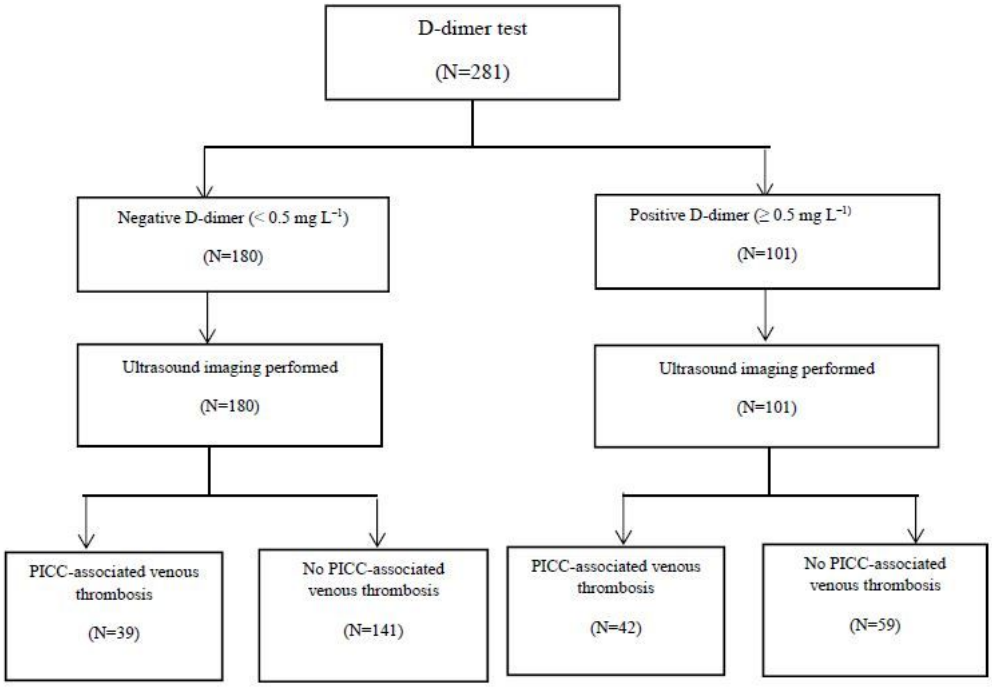

Figure 3